

REMARKS

Claims 1-5 are pending. Claims 1 had been amended and claim 2 is cancelled herein.

Support for the amendments to claim 1 can be found in the specification as filed, for example, at page 5, line 25 to page 6, line 26, and in the originally filed claims 2.

Applicants respectfully submit that no new matter is introduced.

Response to Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1-5 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Examiner, the phrase “formulated with two active ingredients” is allegedly indefinite “because it is unclear if Applicant intends for the claimed pharmaceutical composition to be defined using product-by-process construction ... or if it is intended to be a definition of what is contained therein the claimed pharmaceutical composition rather than how it is formulated.” (Office Action, 3). In addition, the Examiner contends that “it is unclear if Applicant intends for the composition to be closed or open to additional elements.” (Office Action 3-4). Without acquiescing in these rejections, and solely to expedite allowance of the claims, Applicants have amended claim 1 to remove the recitation of “formulated....” and to simply recite the components of the pharmaceutical composition. In view of the claim amendments, Applicants respectfully submit that the Examiner’s § 112 rejections to claims 1-5 are moot.

Rejection under 35 U.S.C. § 103

The Examiner also rejects claims 1-5 under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,989,578 to Bernat et al. (“Bernat”) in view of Asai et al..

Annual Report of Sankyo Research Laboratories, 1999, vol. 51, pp. 1-44 (“Asai”) and U.S. Patent No. 5,288,726 (Koike, *et al*). The Examiner contends that Bernat “teaches a pharmaceutical composition comprising clopidogrel with aspirin, each being present in the free form or in the form of a pharmaceutically acceptable salt (abstract), wherein the composition has anti-platelet aggregation activity (col.1, 1.5-8).” (Office Action, page 4). According to the Examiner “[o]ne of ordinary skill in the art at the time of the invention would have found it prima facie obvious to employ the compound CS-747 (also known as 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine) compound, which is disclosed in the prior art as an effective platelet aggregation inhibitor with high potency, fast onset and long duration of action and less toxicity as compared to clopidogrel as evidenced by Asai et al., in place of the clopidogrel compounds of the pharmaceutical composition of Bernat et al, to elicit the predictable result of producing a pharmaceutical composition with platelet aggregation inhibitory activity, but with the advantage of having a more rapid onset of action, longer duration of action and reduced toxicity” (Office Action, page 5).

Applicants respectfully traverse the Examiner’s ground of rejection for at least the reasons that one of ordinary skill in the art would not have had a reasonable expectation that Applicants’ invention would successfully provide a clinical benefit that would outweigh potential risks and that the claimed methods provide unexpected results in (a) providing a clear synergistic effect against thrombosis *in vivo*, (b) providing a superior net clinical benefit over the combination of clopidogrel and aspirin, (c) providing an unexpectedly enhanced benefit to diabetes mellitus patients, which is not observed with clopidogrel and aspirin, and (d) surprisingly addressing interpatient variability of response to clopidogrel and aspirin.

One Skilled in the Art Would Not Have Had a Reasonable Expectation of Success

There is ample evidence in the art that demonstrate that at the time of Applicants' invention, one of ordinary skill in the art would not have had a reasonable expectation that Applicants' invention would successfully provide clinical benefits that would outweigh potential risks. Applicants submit herewith a declaration of Paul A. Gurbel, M.D. under 37 CFR §1.132. Dr. Gurbel's declaration shows that as of the filing date of the present application, "one skilled in the art would not have had a reasonable expectation that the combination of aspirin and prasugrel would exhibit a clinical benefit that would outweigh the risk of potentially dangerous bleeding." Gurbel Decl., ¶ 20.

Dr. Gurbel is a practicing clinician with considerable experience using anti-platelet therapy. Dr. Gurbel has been a practicing interventional cardiologist since 1990 and is currently the Director for the Center for Thrombosis Research at Sinai Hospital in Baltimore, which conducts investigations of platelet physiology and coagulation. Gurbel Decl., ¶ 11. Dr. Gurbel's research focuses on "anti-platelet agents and the relation of platelet reactivity to ischemic event occurrence." Gurbel Decl., ¶ 12. In particular, Dr. Gurbel's laboratory has been "recognized in the field for its studies in antiplatelet drug effects and resistance to antiplatelet drug therapy." Gurbel Decl., ¶ 12. In particular, Dr. Gurbel's laboratory was "the first to demonstrate the relation between high platelet reactivity to adenosine phosphate (ADP) and ischemic event occurrence in patients undergoing percutaneous coronary intervention (PCI)." Gurbel Decl., ¶ 12. Additionally, Dr. Gurbel is "a faculty member in the Cardiology Division of the Johns Hopkins University, which is one of the top 50 U.S. Hospital Heart Programs as rated by the U.S. News and World Report, and am appointed as Associate Professor of Medicine at the Johns Hopkins University School of Medicine in Baltimore, Maryland." Gurbel Decl., ¶ 14. Dr.

Gurbel is also “a faculty member at the Sinai Hospital in Baltimore, Maryland.” Gurbel Decl., ¶ 14.

According to Dr. Gurbel, the ACC/AHA guidelines (which are the accepted standard of practice for one or ordinary skill in the art) at the time of invention indicated that “the standard of care at the time of invention was to administer either aspirin or a thienopyridine, but not both.” Gurbel Decl., ¶ 21. In addition, Dr. Gurbel states that aspirin was associated with numerous serious contraindications, including intolerances, allergy, active bleeding, hemophilia, retinal bleeding, severe untreated hypertension, active peptic ulcer or other serious gastrointestinal or genitourinary bleeding. See Gurbel Decl., ¶¶ 28-29. Particularly, Dr. Gurbel explains that patients treated with aspirin are significantly more likely to suffer GI bleeding and hemorrhagic strokes. See Gurbel Decl., ¶29. As stated by Dr. Gurbel, “[i]n view of the risks associated with inhibition of the COX-1 enzyme by aspirin, each of the three guidelines from at or around the time of invention recommended that thienopyridines be administered as alternatives to, and not adjuncts with aspirin.” Gurbel Decl., ¶31. According to Dr. Gurbel although beneficial effects may be obtained from treatment with ticlopidine and clopidogrel, both of those compounds were at the time of Applicants’ priority applications associated with significant risks. See Gurbel Decl., ¶¶32-36. In fact, Dr. Gurbel states that it was recognized in the art that bleeding is a complication of antiplatelet treatment. Gurbel Decl., ¶35.

The significant activity of each of the thienopyridines and aspirin alone, and their associated risks, particularly as they are related to an increased potential for serious bleeding prevented those skilled in the art from having a reasonable expectation of successful combination therapy with prasugrel and aspirin. As explained by Dr. Gurbel, “[i]n 2000, it was still not known whether the combined administration of a thienopyridine (e.g., ticlopidine or clopidogrel)

and aspirin provided a clinical benefit over aspirin alone....” Gurbel Decl., ¶37. Dr. Gurbel states at that time, it was unclear whether combination of aspirin and ticlopidine provided any significant clinical benefit, but it had already been shown to significantly increase risk of hemorrhagic and vascular surgical complications. Gurbel Decl., ¶38. More particularly, Dr. Gurbel notes that the safety of PLAVIX (the proprietary name for clopidogrel) in combination with aspirin had not yet been established at the time of invention. Gurbel Decl., ¶39. Instead, there was a concern about significant hemorrhagic risks related to the combination, and therefore, aspirin was not even recommended to be used in conjunction with PLAVIX. See Gurbel Decl., ¶¶36-40. Therefore, Dr. Gurbel opines that “as of December 25, 2000, the art recognized significant potential risks associated with administration of a thienopyridine, such as ticlopidine or clopidogrel, with aspirin, and could not have predicted whether the potential benefits provided by such a combination would outweigh the potential risks.” Gurbel Decl., ¶43.

Moreover, at the end of 2000, it was not known whether substituting prasugrel for clopidogrel or ticlopidine in combination with aspirin would provide any clinical benefit, much less one that outweighs the potential bleed risks. Dr. Gurbel explains that at the time of Applicants’ priority application, it was not known whether or not prasugrel could potentially provide clinical benefits that would outweigh potential risks. See Gurbel Decl., ¶¶44-45. Dr. Gurbel also states that “[s]tudies prior to December 2000 indicate that inhibition of signaling via the P2Y₁₂ receptor can also block signaling through the thromboxane A₂ (TXA₂) pathway, which is the pathway through which aspirin acts.” Gurbel Decl., ¶46. According to Dr. Gurbel, “[i]n view of the understanding in 2000 of the receptor signaling involved in platelet aggregation and the potency of prasugrel to block P2Y₁₂ signaling, one skilled in the art would have doubted whether adding aspirin to prasugrel would have significantly increased its anti-thrombotic

effect.” Gurbel Decl., ¶47. Therefore, Dr. Gurbel concludes that “[i]t was unknown whether prasugrel and aspirin would provide a sufficient net clinical benefit over prasugrel alone or over aspirin alone and the risk of bleeding with prasugrel and aspirin at that time was entirely unknown.” Gurbel Decl., ¶48.

As explained by Dr. Gurbel, as of December 25, 2000 “one skilled in the art would not have reasonably relied on data from administration of ticlopidine or clopidogrel to predict the efficacy or safety of prasugrel in combination with aspirin....” Gurbel Decl., ¶50. In addition, Dr. Gurbel explains that there were numerous different drugs that inhibit platelet activity and thrombus formation, and therefore, one skilled in the art would not have necessarily substituted prasugrel in place of either ticlopidine or clopidogrel. See Gurbel Decl., ¶¶55-58. According to Dr. Gurbel, “one skilled in the art would have had a large number of potential antithrombotic agents from which to choose and would not have necessarily substituted prasugrel in place of either ticlopidine or clopidogrel.” Gurbel Decl., ¶58. Moreover, as explained above and by Dr. Gurbel, it is the activity of the combination of prasugrel and aspirin together and the potential for the combination to contribute to excessive bleeding risk that prevents one skilled in the art from having a reasonable basis for expecting the combination to be successful.

Unexpected Results

As explained in the Gurbel declaration, the specification of the present application demonstrates that the combination of prasugrel and aspirin provide a clear synergistic effect against thrombosis *in vivo*. Gurbel Decl., ¶59. Specifically, Table 1 of the specification shows that the combination of prasugrel and aspirin provides a greater rate of inhibition against

thrombus formation than the sum of the effect of each of the components alone. See Gurbel Decl., ¶¶60.

Additionally, Dr. Gurbel states that “one skilled in the art would not have had any expectation that the combination of prasugrel and aspirin would provide clinical benefits that would outweigh the bleeding risks associated with administration of both prasugrel and aspirin.” Gurbel Decl., ¶¶61. This superior net benefit could not have been expected by one skilled in the art as of the filing date of the present application. In fact, Asai et al. report that “CS-747 was the most potent in the prolongation of bleeding time,” but that “CS-747 and clopidogrel may comparatively have similar ratios of benefit/bleeding risk.” *Id.* at 16. Citing to a large scale clinical study (TRITON-TIMI 38), Dr. Gurbel states that this is further evidence of “the superior clinical benefits provided by the administration of a combination of prasugrel and aspirin as compared to combination of clopidogrel and aspirin.” Gurbel Decl., ¶¶62-63. Specifically, the study showed superior results for prasugrel and aspirin in the rate of the primary efficacy end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), myocardial infarction (MI), urgent target-vessel revascularization, stent thrombosis, recurrent myocardial infarction followed by death from cardiovascular disease. Gurbel Decl., ¶¶62. In addition, Dr. Gurbel explains that the bleeding risk for prasugrel in combination with aspirin was surprisingly lower than expected as compared to clopidogrel and aspirin. See Gurbel Decl., ¶¶68-70. In fact, even in 2009, Dr. Gurbel had “expected that prasugrel with aspirin would increase bleeding in these patients more than it actually did.” Gurbel Decl., ¶¶70.

Additionally, the clinical benefits of prasugrel in combination with aspirin were generally and unexpectedly even more pronounced in patients having diabetes mellitus (DM). Specifically, Dr. Gurbel explains that prasugrel and aspirin surprisingly provide increased benefit

in patients with diabetes mellitus (DM) as compared to clopidogrel and aspirin in the primary end point, myocardial infarction (MI), and stent thrombosis. Gurbel Decl., ¶83. As stated by Dr. Gurbel “the combination of prasugrel and aspirin provides an unexpected result in an enhanced benefit to a population of patients that had not previously demonstrated a distinction when treated with clopidogrel and aspirin.” Gurbel Decl., ¶84.

Interpatient Variability of Clopidogrel and Aspirin

Combined administration of clopidogrel and aspirin results in considerable heterogeneity in the response by individual patients. For example, studies have estimated that adequate platelet effects are not achieved in 5% to 45% of patients taking aspirin and 4% to 30% of patients taking clopidogrel (see, for example, Lev et al., “Aspirin and Clopidogrel Drug Response in Patients Undergoing Percutaneous Coronary Intervention,” Journal of the American College of Cardiology, 47(1):27-33 (2006)(attached Exhibit A). Studies have also found that about 50% of patients who are aspirin resistant are also resistant to clopidogrel. See, for example, Lev, p. 29, right column: “Regardless of which aspirin resistance definition was used, about 50% of patients who were aspirin resistant were also resistant to clopidogrel.”

The interpatient variability of each of clopidogrel and aspirin were reported prior to the filing date of the present application in Van De Graaff et al., “Variable Interindividual Responses to Antiplatelet Therapies- Do They Exist, Can We Measure Them, and Are They Clinically Relevant?” Heart Drug, 1(1):35-43 (2001)(“Van De Graff”)(attached as Exhibit B), which was made available online as of August 2000. With respect to aspirin, Van De Graaff describes that “platelet function studies reveal a significant variation in an individual’s response to aspirin and suggest that a subset of the population might be resistant to the drug’s protective effects against

thromboembolic complications.” Id. at 39. For example, Van De Graaff reported in a clinical trial assessing long-term cardiovascular events that “8-12% of patients taking aspirin do not achieve the therapeutic benefit of platelet inhibition, based on aggregometry.” Id. Van De Graaf also reported substantial variation in aggregation response to ADP for ticlopidine and clopidogrel. For example, Van De Graaff reports that “15% of specimens revealed increased aggregation with ticlopine” and that clopidogrel demonstrated a large range of variability, $\pm 27\%$ from the mean. See id. In view of this data, Van de Graaff reported that “[a]lthough not as well studied as with aspirin, interindividual variability has also been observed in platelet reactivity during treatment with this class of medication,” referring to the class of thienopyridines. Id. Additionally, Van de Graaff reports that:

Variable degrees of platelet blockade, based on in vitro assays of platelet function, have been consistently demonstrated in persons taking aspirin, thienopyridines and GP IIb/IIIa inhibitors.

(Id., p. 41, right column, ll. 30-34). By specifically referring to the class of thienopyridines as being associated with interindividual variability, Van de Graaff removes any basis for one skilled in the art of having a reasonable expectation that prasugrel, another thienopyridine, would behave differently and be able to treat individuals who are unresponsive to clopidogrel. The variability in response reported earlier by Van de Graaff has continued to be confirmed for combinations of clopidogrel and aspirin.

Because of significant populations of patients for whom prior combinations did not provide adequate therapy, the art recognized the need for new alternatives to treat patients exhibiting resistance to clopidogrel/aspirin. See, for example, Van de Graaff, which states that

Importantly, clinical trials have not uniformly supported the rationale of using higher dosing of antiplatelet medication to overcome the effect of drug resistance

[20-23]. These data suggest that alternative methods of platelet blockade must be sought for patients resistant to all doses of conventional antiplatelet medication. (Van de Graaff, p. 41, right column, ll. 21-27). Since the problem of drug resistance is not overcome simply by increasing the dose of antiplatelet medication, the art was without any obvious solution to treat drug-resistant individuals.

The problem of inconsistent response (i.e., high interindividual variability in response) is clinically relevant because studies have shown that dual drug-resistant patients have a more than two-fold increase in the rate of myonecrosis compared with drug-sensitive patients, as well as higher marker levels associated with higher risk of death, myocardial infarction, and repeat revascularization for patients following certain undergoing dual antiplatelet therapy. See, for example, Lev, p. 32, paragraph bridging left and right columns: “We evaluated the incidence of CK-MB elevation following PCT, which has been consistently shown to be associated with higher risk of death, MI, and repeat vascularization.” In another study, aspirin-resistant patients had a 2.9-fold increased risk of CK-MB elevation compared with aspirin-sensitive patients, where CK-MB elevation is associated with a higher risk of death, among other poor clinical outcomes (see Chen et al., “Aspirin resistance is associated with a higher incidence of myonecrosis after nonurgent percutaneous coronary intervention despite clopidogrel pretreatment,” J Am Coll Cardiol, 43:1122-6, 1125 (2004)(attached as Exhibit C)). The clinical relevance of resistance was also appreciated at least as of August 2000, where Van de Graaff states that “[s]mall studies have suggested the clinical importance of this resistance to therapy in aspirin-treated patients,” (see Van de Graaff, p. 41, right column, ll. 34-35).

The variable response to treatment with clopidogrel and aspirin leaves a subpopulation of patients subject to continued risks for cardiovascular events creating an unmet need.

unexpectedly met by prasugrel and aspirin. For example, the European Medicines Agency (EMA) report notes that “it has been shown that ‘non-responsiveness’ to a clopidogrel 600 mg LD is a strong predictor of stent thrombosis in patients receiving drug-eluting stents, and in addition, that residual platelet aggregation above the median is associated with a 6.7-fold increased risk of major cardiac events (death, myocardial infarction and target vessel revascularisation) at 1 month follow-up in patients undergoing elective PCI.” EMA Assessment Report for Efient, Doc. Ref. EMA/117561/2009 at page 4 (“EMA Report”)(attached as Exhibit D). Moreover, the variable response to treatment with clopidogrel and its use in combination with aspirin has been recognized in “[a] growing number of studies [that] have linked poor antiplatelet response to clopidogrel to adverse clinical outcomes, particularly coronary ischemia and stent thrombosis.” Wiviott et al., “Prasugrel,” Circulation, 122: 394-403 (2010)(“Wiviott Review”)(attached as Exhibit E).

For example, the variability of clopidogrel inhibition of ADP-induced platelet aggregation range “from less than 10% to almost complete inhibition of platelet aggregation with a wide distribution across this range....” Holmes et al., “ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA ‘Boxed Warning.’ A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association,” Circulation, 122: 537-557, 539 (2010)(“Holmes”)(attached as Exhibit F). The reference also reports that this uncontrolled residual platelet reactivity is “associated with an increased risk of cardiac, cerebrovascular, and peripheral arterial events.” Id. at 539. In another example, Lev reports considerable heterogeneity in the responses of individual patients to aspirin, particularly that “studies have estimated that adequate antiplatelet effects are not achieved in 5% to 45% of patients taking aspirin and 4% and 30% of patients taking

clopidogrel.” Id. As reported in Lev, “[r]esistance to the antiplatelet effects of aspirin has been associated with adverse clinical outcomes and with an increase in markers of myonecrosis following PCT.” Id.

In view of these significant health risks associated with non-responsiveness to clopidogrel and aspirin, the FDA modified the prescribing information for PLAVIX, the commercially sold drug product that contains the active ingredient clopidogrel, with a black box warning that recommends consideration of alternative treatment or treatment strategies. See PLAVIX label. In response to the black box warning for PLAVIX and recognizing the difficulties clinicians face when dealing with interpatient variability, one of the options recommended by the authors in Roden et al. “Responding to the Clopidogrel Warning by the US Food and Drug Administration: Real Life Is Complicated,” Circulation, 122: 445-448 (2010)(attached as Exhibit G) is to ignore clopidogrel and prescribe prasugrel, which further evidences the unexpected ability to fill an unmet need. See id., at 446.

Reduction in Interpatient Variability

The administration of prasugrel and aspirin surprisingly reduces the interpatient variability of response to treatment with clopidogrel and aspirin. For example, in Jernberg et al., “Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease,” European Heart Journal, 27: 1166-1173 (2006)(attached as Exhibit H), it was reported that “when added to aspirin in patients with stable atherosclerotic disease, prasugrel achieves significantly greater IPA [inhibition of platelet aggregation] with a significantly lower percentage of pharmacodynamic non-responders compared with clopidogrel.” Id. at 1172. In particular,

Jernberg provides experimental data based on the administration of various loading and maintenance doses of clopidogrel and prasugrel to patients who were also administered the same amount of aspirin (325 mg/day of enteric-coated aspirin). See *id.* at 1167, Study Design. According to Jernberg, a group of patients were administered the FDA approved loading and maintenance doses for clopidogrel at an initial loading dose of 300 mg, followed by daily maintenance doses of 75 mg. Another group of patients were administered with prasugrel at a loading dose of 40 mg, followed by daily maintenance doses of 5 mg or 7.5 mg of prasugrel. A further group of patients were administered prasugrel in combination with aspirin at a loading dose of 60 mg, followed by daily maintenance doses of 10 mg or 15 mg of prasugrel.

Inhibition of platelet aggregation was measured using two different assays and non-responders for each assay were reported in Figures 4(A) and 4(B). The data reported in Figure 4(A) was generated using 5 μ M of ADP as an agonist to induce platelet aggregation, and non-responders were defined as those patients who achieved <25% response. The data reported in Figure 4(B) was generated using 20 μ M of ADP as an agonist to induce platelet aggregation, and a non-responder was defined as those patients who achieved <20% response.

As can be seen in Figures 4(A) and 4(B), only 0% or 3% of patients administered with loading doses of 40 mg or 60 mg prasugrel in combination with aspirin were considered as non-responders, while 26% of patients administered with the clopidogrel and aspirin combination were considered as non-responders (< 25% response) to 5 μ M of ADP as an agonist and 52% of the clopidogrel and aspirin combination were considered as non-responders (< 20% response) to 20 μ M of ADP as an agonist. In addition, after administration of maintenance doses for 28 days, consistently less percentage of patients administered with prasugrel and aspirin at all of the tested doses (*i.e.*, 5mg, 7.5mg, 10mg and 15mg) were considered as non-responders as compared

to those patients administered with a maintenance dose of 75 mg clopidogrel with aspirin. In addition, Jernberg reports that:

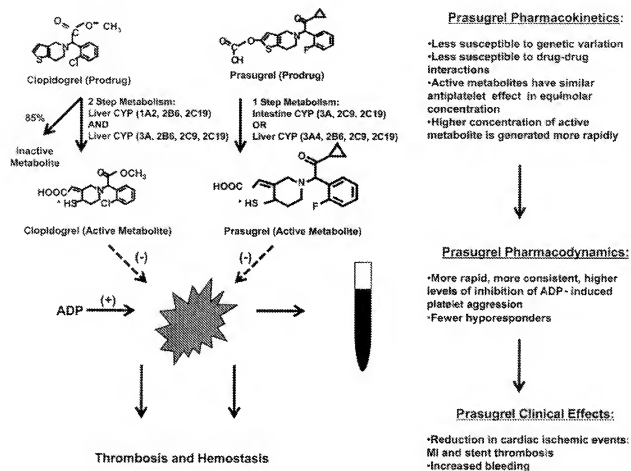
Using the Δ MPA criteria for non-responders reported by Gurbel et al. the percentage of clopidogrel nonresponders in this study is lower and comparable to the literature (~20% non-responders with the clopidogrel 300 mg LD and 30% with the clopidogrel 75 mg MD), reflecting the lower threshold of platelet inhibition required to be considered a pharmacodynamic responder to clopidogrel with this criteria. Similar to the results obtained using the model-based approach in the current study, the percentage of non-responders for prasugrel using Gurbel's definition was still only 3% in the prasugrel 40 and 60 mg LD groups (and 0, 0, 10, and 20% at the prasugrel MDs of 15, 10, 7.5, and 5.0 mg, respectively

(Jernberg, 1171). Accordingly, Jernberg itself reaches the conclusion that the combination of prasugrel and aspirin for all of the dosages shown in Figure 4 unexpectedly overcomes the interpatient variability previously observed for clopidogrel and aspirin. Therefore, this data provides important evidence that methods of administering prasugrel and aspirin surprisingly provide a more consistent response in the treatment of non-responding patients with antiplatelet therapy.

Genetic Variability in Patients

As further discussed in the Gurbel declaration, “[i]t has been found that one possible explanation for the differences in the interpatient variability of clopidogrel in combination with aspirin as compared prasugrel in combination with aspirin is the inability of certain patients to metabolize clopidogrel, which is a prodrug, into its active form.” Gurbel Decl., ¶78. This genetic variation further explains that the unexpected results seen in the Jernberg reference (i.e., prasugrel in combination with aspirin overcomes the interpatient variability previously observed for clopidogrel and aspirin) is not limited to those dosages tested.

Metabolism of both clopidogrel and prasugrel are shown in the figure reproduced from the Wiviott Review below:



The Wiviott Review reports that, “[t]he CYP enzymes involved in [the] conversions [of prasugrel and clopidogrel into their active forms] are known to be subject to common genetic variation resulting in differential function.” *Id.* at 399. As summarized by the Wiviott Review, “several studies have reported that patients who are carriers of a reduced-function allele of CYP 2C19 are at increased risk of recurrent cardiovascular events, including MI and stent thrombosis, while being treated with clopidogrel.” *Id.* In particular, the Wiviott Review reports that “[a]mong the clopidogrel subjects, carriers had an excess of cardiovascular ischemic events, including a 3-fold higher rate of stent thrombosis. *Id.* at 399. As reported by Holmes:

There are genetic polymorphisms in several CYP450 enzymes involved in the metabolism of clopidogrel, but variants in CYP2C19, particularly CYP2C19*2, are reproducibly associated with variability in clopidogrel active metabolite bioavailability, antiplatelet effects, and clinical outcomes. The **CYP2C19*2 variant** encodes a nonfunctional protein. There are ethnic differences in its distribution; approximately 50% of Chinese, 34% of African Americans, 25% of Whites, and 19% of Mexican Americans carry at least 1 copy of the reduced function CYP2C19*2 allele. Other genetic polymorphisms associated with impaired CYP2C19 activity and possibly adverse clinical events (CYP2C19*3, *4, *5, *8) are much less common in Whites, African Americans, and Hispanics. The number of reduced function alleles is important: individuals with **1 variant allele** (intermediate metabolizers) had **26% to 31% lower exposure** to the active metabolite of clopidogrel, and those with **2 genetic polymorphisms** (poor metabolizers) had **46% to 55% lower exposure** compared with those with no CYP2C19 polymorphisms.

Id. at 539-540 (emphasis added). A study based on a large scale clinical study, TRITON-TIMI 38 Trial, reported in Mega et al., “Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis,” Lancet (Published online August 29, 2010)(“Mega”)(attached as Exhibit I), provides additional experimental data supporting this genetic basis for the significant interpatient variability for patients administered clopidogrel and confirms that this deficiency is not applicable to prasugrel. As reported in Mega:

...none of the common variants in the CYP genes tested showed consistent reductions in prasugrel active metabolite generation and the antiplatelet effects of prasugrel. Consequently, subjects assigned to prasugrel in the TRITON-TIMI 38 genetic analysis had no difference in the rates of cardiovascular ischemic events by genotype suggesting that the more efficient metabolism of prasugrel may render patients less susceptible to such genetic variation. Id. at 1.

Applicants respectfully submit that it is unexpected that the combination of prasugrel and aspirin would overcome this genetic variation and address the problem of non-responders to clopidogrel and aspirin.

As Dr. Gurbel states in his declaration, “[b]ased on what was known at the priority date, it was unexpected that the combination of prasugrel and aspirin would overcome this genetic

variation and address the problem of non-responders to the combination of clopidogrel and aspirin.” Gurbel Decl., ¶81. This genetic variation, which has a direct impact on the metabolism of prasugrel as compared to clopidogrel, is not limited only to those dosages presented in the Jernberg reference.

Summary

In summary, Applicants respectfully traverse the Examiner’s rejection for at least the reason that one of ordinary skill in the art would not have had a reasonable expectation that Applicants’ invention would successfully provide a clinical benefit that would outweigh potential risks. In particular, Dr. Gurbel opines that:

- As of December 25, 2000, one skilled in the art would not have had a reasonable expectation that the combination of aspirin and prasugrel would exhibit a clinical benefit that would outweigh the risk of potentially dangerous bleeding;
- As of December 25, 2000, one skilled in the art would not have reasonably relied on data from ticlopidine or clopidogrel to predict the efficacy or safety of prasugrel in combination with aspirin; and
- As of December 25, 2000, a physician had a variety of medications from which to choose in order to inhibit platelet activity and thrombus formation and therefore, would not have necessarily substituted prasugrel in place of either ticlopidine or clopidogrel.

Gurbel Decl., ¶9. In addition, Applicants respectfully submit that the claimed methods provide unexpected results. Specifically, Dr. Gurbel opines that:

- The data provided by Table 1 of the specification demonstrate that the combination of prasugrel and aspirin provide a clear synergistic effect against thrombosis *in vivo*, which could not have been expected by one skilled in the art as of December 25, 2000;
- The combination of prasugrel and aspirin provides superior net clinical benefits over the combination of clopidogrel and aspirin, which could not have been expected by one skilled in the art as of December 25, 2000;
- The combination of prasugrel and aspirin surprisingly addresses interpatient variability of response to clopidogrel and aspirin, which could not have been expected by one skilled in the art as of December 25, 2000; and

- The combination of prasugrel and aspirin provides unexpectedly superior results as compared to the combination of clopidogrel and aspirin in patients with diabetes mellitus.

Gurbel Decl., ¶9. Furthermore, the Jernberg reference provides evidence that the administration of prasugrel and aspirin surprisingly reduces the interpatient variability of response to treatment with clopidogrel and aspirin.

In view of all of the above, Applicants respectfully request withdrawal of the §103 rejections.

Related Applications

The Examiner requests that the Applicant “provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application.” (Office Action, 7). Applicants bring to the Examiner’s attention a Related Case Submission submitted on October 27, 2009 and considered by the Examiner on August 13, 2010 in the present application. The previously submitted Related Case Submission lists Application Serial Nos. 11/520,168 and 12/006,546. For the Examiner’s convenience an additional Related Case Submission is provided herewith identifying these two applications.

CONCLUSION

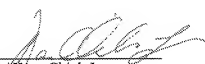
Based on the foregoing remarks, Applicants respectfully request withdrawal of all rejections and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this response to Deposit Account No. **50-3732**, Order No. 17620.105003. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 17620.105003.

Respectfully submitted,
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